
Endogenous mammalian histone H3.3 exhibits chromatin-related functions during development.

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Public Summary:

BACKGROUND: The histone variant H3.3 plays key roles in regulating chromatin states and transcription. However, the role of endogenous H3.3 in mammalian cells and during development has been less thoroughly investigated. To address this gap, we report the production and phenotypic analysis of mice and cells with targeted disruption of the H3.3-encoding gene, H3f3b. **RESULTS:** H3f3b knockout (KO) mice exhibit a semilethal phenotype traceable at least in part to defective cell division and chromosome segregation. H3f3b KO cells have widespread ectopic CENP-A protein localization suggesting one possible mechanism for defective chromosome segregation. KO cells have abnormal karyotypes and cell cycle profiles as well. The transcriptome and euchromatin-related epigenome were moderately affected by loss of H3f3b in mouse embryonic fibroblasts (MEFs) with ontology most notably pointing to changes in chromatin regulatory and histone coding genes. Reduced numbers of H3f3b KO mice survive to maturity and almost all survivors from both sexes are infertile. **CONCLUSIONS:** Taken together, our studies suggest that endogenous mammalian histone H3.3 has important roles in regulating chromatin and chromosome functions that in turn are important for cell division, genome integrity, and development.

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